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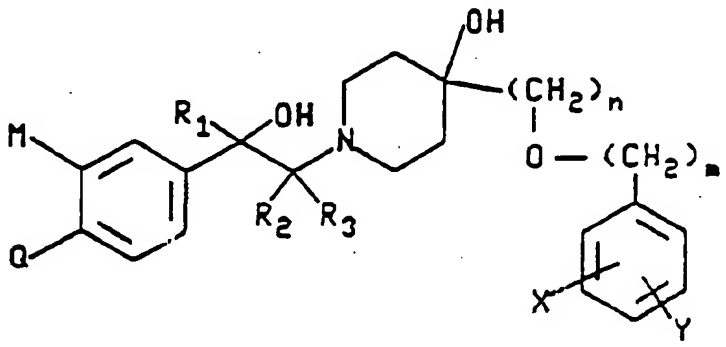
(54) Title: 2-(4-HYDROXYPIPERIDINO)-1-ALKANOL DERIVATIVES AS ANTIISCHEMIC AGENTS



(I)

(57) Abstract

A series of 2-(4-hydroxypiperidino)-1-alkanol derivatives (I) are useful as medicaments for the treatment of traumatic injuries to the brain and spinal cord and neuronal degenerative diseases including senile dementias, in mammals, especially humans.

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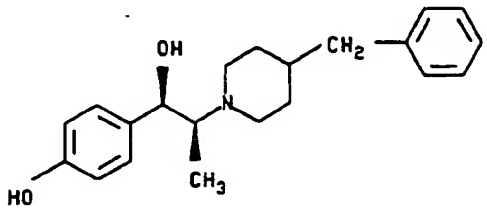
2-(4-HYDROXYPIPERIDINO)-1-ALKANOL DERIVATIVES AS ANTIISCHEMIC AGENTS

BACKGROUND OF THE INVENTION

The present invention is directed to neuroprotective (antiischemic excitatory amino acid receptor blocking) 2-(4-hydroxypiperidino)-1-alkanol derivatives defined by formula (I) below; pharmaceutically acceptable salts thereof; a method of using these compounds in the treatment of stroke, traumatic injury to the brain and spinal cord, and neuronal degenerative diseases including (but not limited to) senile dementias such as Alzheimer's disease, Huntington's disease and Parkinson's disease in mammals, especially humans; and to certain intermediates therefor.

Ifenprodil (A) is a racemic, so-called dl-erythro compound having the relative stereochemical formula



---(A)

which is marketed as a hypotensive agent, a utility shared by a number of close analogs. Carron et al., U.S. Patent 3,509,164; Carron et al., Drug Res., v. 21, pp. 1992-1999 (1971). More recently, ifenprodil has been shown to possess antiischemic and excitatory amino acid receptor blocking activity. Gotti et al., J. Pharm. Exp. Therap., v. 247, pp. 1211-21 (1988); Carter et al., loc. cit., pp. 1222-32 (1988).

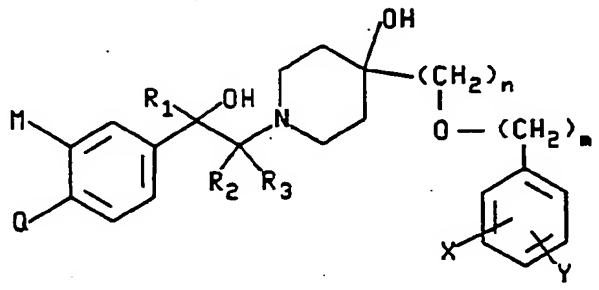
See also French Patent 2546166 and EPO publication EP-A1-351282, published January 17, 1990. A goal, substantially met by the present invention, has been to

find compounds possessing neuroprotective activity in good measure, while at the same time having lowered or no significant hypotensive effect.

Certain 1-phenyl-3-(4-aryl-4-acyloxy-piperidino)-1-propanols have also been reported to be useful as analgesics, U.S. Patent 3,294,804; 1-[4-(amino-and hydroxy-alkyl)phenyl]-2-(4-hydroxy-4-tolylpiperazino)-1-alkanols and alkanones have been reported to possess analgesic, antihypertensive, psycho- tropic or antiinflammatory activity, Japanese Kokai 53-02,474 (CA 89:43498y; Derwent Abs. 14858A) and 53-59,675 (CA 89:146938w; Derwent Abs. 48671A); and 2-piperidino-1-alkanol derivatives have been reported to be active as antiischemics, EP 398,578-A and Der 90-350,327/47.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of the formula



(I)

wherein R_1, R_2 and R_3 are each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on

said substituted phenyl is selected from the group consisting of hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, amino, nitro and alkoxy having 1 to 4 carbons;

or R_1 and R_2 when taken together form a methylene, ethylene, propylene or butylene group;

m is 0 to 2;

n is 1 or 2;

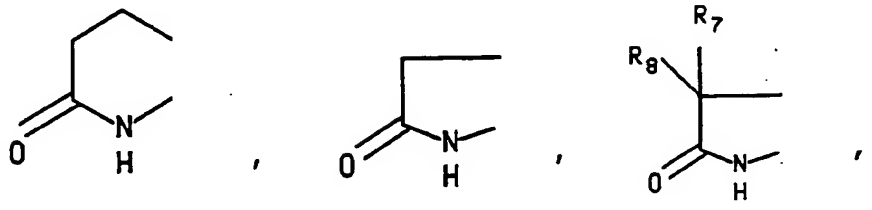
X and Y are each selected from the group consisting of hydrogen, chloro, bromo, fluoro, trifluoromethyl, alkoxy having 1 to 4 carbons, alkyl having 1 to 4 carbons, hydroxy, amino, nitro and substituted phenoxy, wherein the substituent on said substituted phenoxy is selected from the group consisting of hydrogen, hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, nitro, amino and alkoxy having 1 to 4 carbons;

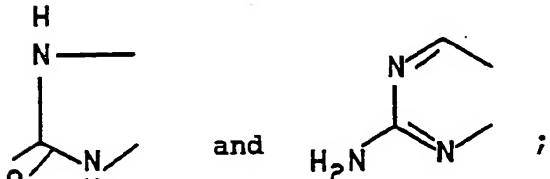
M and Q are each selected from the group consisting of hydrogen, hydroxy, amino, chloro, bromo, fluoro, trifluoromethyl, nitro, alkyl having 1 to 4 carbons, alkoxy having 1 to 4 carbons, N,N-dialkylamino having 1 to 4 carbons in each of said alkyls, N-alkylamino having 1 to 4 carbons, $NHCOR_4$, $NHCOOR_5$ and $NHSO_2R_6$;

wherein R_4 is selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

and wherein R_5 and R_6 are each selected from the group consisting of alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino,

nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;
or M and Q when taken together form a divalent radical Z, wherein Z is selected from the group consisting of





and

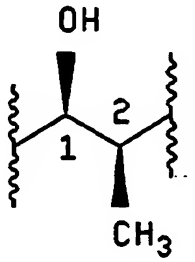
;

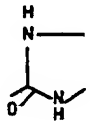
wherein R_7 and R_8 are each selected from the group consisting of hydrogen and methyl;
and the pharmaceutically acceptable acid addition salts of these compounds.

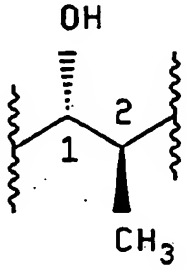
The expression "pharmaceutically acceptable acid addition salts" is intended to include but is not limited to such salts as the hydrochloride, hydrobromide, hydroiodide, nitrate, hydrogen sulfate, dihydrogen phosphate, mesylate, maleate, and succinate. Such salts are conventionally prepared by reacting the free base form of

the compound (I) with an appropriate acid, usually one molar equivalent, and in a solvent. Those salts which do not precipitate directly are generally isolated by evaporation of the solvent and/or addition of a non-solvent followed by filtration.

A preferred group of compounds of the present invention are those in which M and Q form a radical Z, wherein Z is  , R_1 and R_2 are hydrogen and R_3 is methyl and the compounds possess 1r*, 2s* or erythro relative stereochemistry at the 1- and 2-positions of the propanol chain, i.e.,

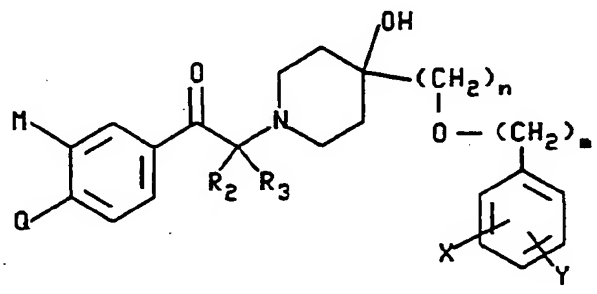


A second preferred group of compounds of this invention are those in which M and Q form a radical Z, wherein Z is  , R_1 and R_2 are hydrogen and R_3 is methyl and the compounds possess 1s*, 2s* or threo relative stereochemistry at the 1- and 2- positions of the propanol chain, i.e.,



The present invention is also directed to pharmaceutical compositions containing a compound of the invention of formula I, and to methods of treating a mammal, particularly human subject, suffering from a central nervous disorder, which comprises administering to said mammal a neuroprotective effective amount of a compound of the formula (I). Said compositions and methods are particularly valuable in the treatment of traumatic injury to the brain and spinal cord, stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease and related disorders of the central nervous system.

The present invention is further directed to intermediate compounds of the formula



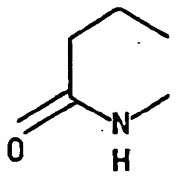
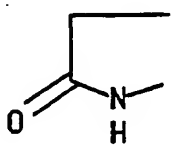
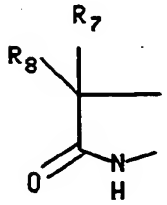
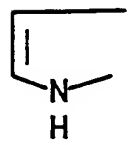
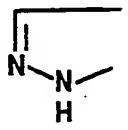
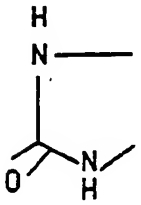
(IV)

wherein

R_2 and R_3 are each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, alkyl having 1 to 4 carbons, chloro, bromo,

fluoro, trifluoromethyl, amino, nitro and alkoxy having 1 to 4 carbons;
m is 0 to 2;
n is 1 or 2;
X and Y are each selected from the group consisting of hydrogen, chloro, bromo, fluoro, trifluoromethyl, alkoxy having 1 to 4 carbons, alkyl having 1 to 4 carbons, hydroxy, amino, nitro and substituted phenoxy, wherein the substituent on said substituted phenoxy is selected from the group consisting of hydrogen, hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, nitro, amino and alkoxy having 1 to 4 carbons;
M and Q are each selected from the group consisting of hydrogen, hydroxy, amino, chloro, bromo, fluoro, trifluoromethyl, nitro, alkyl having 1 to 4 carbons, alkoxy having 1 to 4 carbons, N,N-dialkylamino having 1 to 4 carbons in each of said alkyls, N-alkylamino having 1 to 4 carbons, $NHCOR_4$, $NHCOOR_5$ and $NHSO_2R_6$;
wherein R_4 is each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;
and wherein R_5 and R_6 are each selected from the group consisting of alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

or M and Q when taken together form a divalent radical Z, wherein Z is selected from the group consisting of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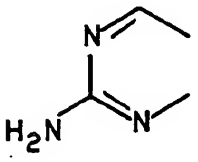

;

and wherein R_7 and R_8 are each selected from the group consisting of hydrogen and methyl.

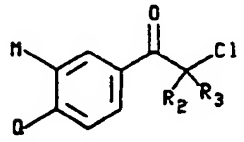
Depending on the precise values of R_1, R_2 and R_3, the compounds of formula (I) can have one or two asymmetric centers, and can therefore exist in various isomeric forms. All such isomers are within the scope of this invention. The individual isomers can be separated by classical methods well-known to those skilled in the art.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention, having the formula (I) defined above, are readily and generally

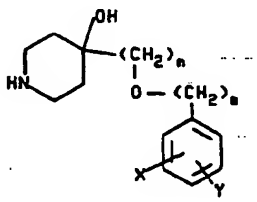
prepared by reaction of chloro compound (II) with piperidine (III), followed by reduction of the resulting ketone (IV) to an alcohol as detailed below.

The precursor ketones are generally initially prepared with -OH and $-NH_2$ substituent groups in protected form, i.e., as $-OA_1$, or $-NHA_2$ groups in the compounds of formula (IV). A_1 and A_2 are defined below. Such protected ketones are generally formed by reacting an appropriately substituted 2-halo-1-alkanone (II) with an appropriately substituted piperidino derivative (III), e.g.,



(II)

+



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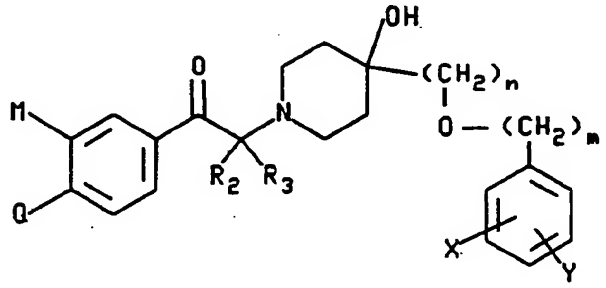


(IV)

Reaction of compound (II) with compound (III) is carried out under conditions typical of nucleophilic displacements in general. Where the two reactants are

about equivalent in availability, close to substantially molar equivalents may be used; although when one is more readily available, it is usually preferred to use that one in excess, in order to force this bimolecular reaction to completion in a shorter period of time. The reaction is generally carried out in the presence of at least 1 molar equivalent of a base, the piperidine derivative itself, if it is readily available, but more usually a tertiary amine which is at least comparable in base strength to the nucleophilic piperidine; and in a reaction inert solvent such as ethanol. If desired, the reaction is catalyzed by the addition of up to one molar equivalent or more of an iodide salt (e.g., NaI, KI). Temperature is not critical, but will generally be somewhat elevated in order to force the reaction to completion within a shorter time period, but not so high as to lead to undue decomposition. A temperature in the range of 50-120°C is generally satisfactory. Conveniently, the temperature is the reflux temperature of the reaction mixture.

As used in the preceding paragraph, and elsewhere herein, the expression "reaction inert solvent" refers to any solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

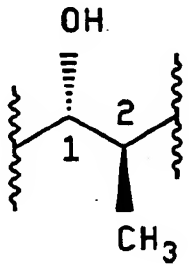
If desired, those ketone intermediates (IV) having OH or NH_2 groups in protected form (OA_1 or NHA_2), can be deprotected at this stage by conventional methods.

For example when A_1 is triisopropylsilyl or tert-butyldimethylsilyl, the protecting group is conveniently removed by reaction with tetrabutylammonium fluoride (generally, substantially 2 molar equivalents) in a reaction inert solvent such as tetrahydrofuran. When A_1 is benzyl or A_2 is benzyloxycarbonyl, the protecting group will generally be removed by conventional hydrogenolysis over a noble metal catalyst in a reaction inert solvent,

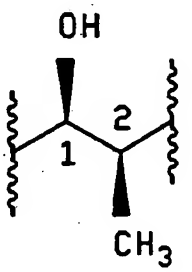
e.g., using 10% Pd/C as catalyst, preferable at low pressures (e.g., 1-10 atmospheres) and temperatures (e.g., 20-75°C) and generally in a reaction inert solvent such as methanol.

Generally, the ketone intermediates (IV) are conveniently converted to corresponding alcohols by one of two conventional reduction methods, to selectively produce either the threo compounds or the erythro compounds of formula (I).

As used in the preceding paragraph, and elsewhere herein, the term "threo" or 1r*, 2s* refers to the relative stereochemistry at the 1- and 2- positions of the propanol chain, i.e.,



and the term "erythro" or 1r*, 2s* refers to the relative stereochemistry at the 1- and 2-positions of the propanol chain, i.e.,



To obtain the desired erythro compounds of formula (I) the corresponding ketone intermediates (IV) are conveniently reduced with potassium borohydride, usually in excess (e.g. greater than 5 mole equivalents), in the presence of glacial acetic acid in a protic solvent such as ethanol, generally at a temperature range of 15-25°C.

To obtain the desired threo compounds of formula (I) the corresponding ketone intermediates (IV) are conveniently reduced with sodium borohydride, usually in excess (e.g. greater than 5 mole equivalents), in a protic solvent such as ethanol, generally at a temperature range of 15-25°C. The resulting reaction mixture is chromatographed on a silica gel column to obtain the said threo compounds of formula (I).

Any protecting groups which are still in place after ketone reduction are then removed according to standard methods described above.

The starting materials and reagents required for the synthesis of the compounds of the present invention are readily available, either commercially, according to literature methods, or by methods exemplified in Preparations below.

The present compounds of the formula (I) possess selective neuroprotective activity, based upon their antiischemic activity and ability to block excitatory amino acid receptors, while at the same time having lowered or no significant hypotensive activity. The antiischemic activity of the present compounds is determined according to one or more of the methods which have been detailed previously by Gotti et al. and Carter et al. cited above, or by similar methods.

The ability of the compounds of the present invention to block excitatory amino acid receptors is demonstrated by the drugs ability to rescue fetal rat neurons in culture which have been exposed to the excitotoxic amino acid glutamate. The following is a typical procedure.

Part I: Cell Isolation:

Embryos at 17 days gestation are removed from rats and placed into Tyrode's solution. The brains are then removed and placed into fresh Tyrode's solution. Using fine iris knives, the hindbrain and thalamus are removed.

The forebrain is then separated into two hemispheres. Next, the meninges are removed gently. The hippocampus appears as a darkened folded area on the inner side of the cortex edge. The hippocampus is carefully cut away from the rest of the tissue and placed in a separate corner of the dish. When all of the dissection is completed, the hippocampal tissue reserved in the corner is minced into 1 mm pieces. These pieces are removed, using a Pasteur pipette and placed into a sterile tube. The Tyrode's solution is aspirated off gently and Calcium-Magnesium Free Tyrode's solution is added. The tissue is washed 3 times with Calcium-Magnesium Free Tyrode's solution. This final wash is incubated 15 minutes at 37 degrees Centigrade. The buffer is again removed and replaced with 1 ml fresh Calcium-Magnesium Free Tyrode's solution. Trypsin is now added at 0.1% (100 µl of a 10 mg/ml stock sterile solution). The tube is incubated for 1 hour at 37 degrees Centigrade. After trypsin incubation the tissue is washed with serum containing medium in order to stop the action of the trypsin. The tissue is resuspended in 1 ml of fresh medium and triturated with a fine bore Pasteur pipette.

Cells are then counted using a hemocytometer. Cells are then seeded onto a 96-well Falcon Primeria tissue culture plates at 75000 cells per well in complete medium. Complete medium is composed of Minimal Essential Medium (MEM) with Earle's salts, 10% Fetal Calf Serum (Hyclone), 10% Equine Serum, L-glutamine (2mM), Penicillin-Streptomycin (100U per ml) and Glucose (to make the final concentration 21 mM a 100x stock containing 27.8 g per 100 ml is prepared). The plates are fed on day 3 with fresh medium. Then on day 6 cytosine arabinoside at 10 µm is added to the cultures with fresh medium. Then two days later the cytosine arabinoside is removed and replaced with Maintenance medium, which is complete medium minus the Fetal Calf Serum. The plates are then fed twice a

week. Three weeks from the time of dissection the plates are used in the glutamate toxicity experiments, in order to insure proper development of the neurons in culture.

Part 2: Glutamate Treatment and Post-Glutamate Drug Addition:

After three weeks in culture, the medium is removed from the cells and the cells are washed three times in chloride free controlled salt solution (CSS-Cl). CSS-Cl contains 69 mM Na_2SO_4, 2.67 mM K_2SO_4, 0.33 mM $NaHPO_4$, 0.44 mM KH_2PO_4, 1 mM $NaHCO_3$, 1 mM $MgSO_4$, 10 mM HEPES (N-2-hydroxyethylpiperazine-N^1-2-ethanesulfonic acid), 22.2 mM glucose, and 71 mM sucrose at pH 7.4. After washing, glutamate is added at 1 to 3 mM in CSS-Cl buffer with appropriate control wells containing buffer without glutamate. The plates are incubated at 37 degrees celsius for 15 to 20 minutes. Following glutamate incubation, the plates are washed with serum free medium twice. The test drugs are prepared at the appropriate concentrations in serum free medium and added to the corresponding wells of the microtiter plate (100 µl per well). Negative control wells receive serum free medium with no drug. Several glutamate treated wells are also given serum free medium with no drug to serve as positive controls. The plate is incubated overnight at 37 degrees celsius and the following day viability is assessed using the LDH (lactate dehydrogenase) and MTT (methyl thiotetrazolinium) assays.

Part 3: Assessment of Cell Viability:

The 100 µl of medium from each plate is removed and transferred to a clean plate to be assayed for the amount of LDH released. Then 100 µl per well of MTT solution is added. This MTT solution is prepared by adding 10 µl of MTT stock (5 mg/ml in PBS, phosphate buffered saline) for every 100 µl serum free medium. Plates are incubated at 37 degrees for 4 to 6 hours. Then 100 µl of acid-alcohol

solution (0.08 N HCl in isopropanol) is added to each well and the wells were mixed vigorously in order to dissolve the purple crystals. Control wells should contain medium with MTT and acid-alcohol, but no cells. The plates are then read on a microplate reader, using a dual wavelength setting test filter at 570 nm and reference filter at 630 nm. The plates must be read within 1 hour.

The medium which is removed is then assayed for LDH. Equal volumes of the samples removed are added to LDH reaction mixture. In this case appropriate wells are pooled to make 500 µl samples. For each sample, reaction mixture is prepared by mixing 480 µl of 0.1 M sodium phosphate buffer, pH 7.5, 10 µl of sodium pyruvate (66 mM) and 10 µl NADH reduced (each vial of NADH containing 5 mg is reconstituted in 440 µl 0.1 N NaOH and 10 µl of this is used per sample). The sample is quickly added to the reaction mixture in cuvettes and the disappearance of absorbance at 340 nm is measured on a Beckman DU-8 spectrophotometer.

Undesired hypotensive activity is also determined by known methods, for example, according to the methods of Carron et al, also cited above.

Such selective neuroprotective antiischemic and excitatory amino acid blocking activities make the compounds of the present invention useful in the treatment of traumatic injury to the brain and spinal cord, degenerative CNS (central nervous system) disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease, without significant potential for concurrent undue drop in blood pressure. In the systemic treatment of such diseases in a human subject with a neuroprotective amount of compounds of the formula (I), the dosage is typically from about 0.02 to 10 mg/kg/ day (1-500 mg/day in a typical human weighing 50 kg) in single or divided doses, regardless of the route of administration. Of course, depending upon the exact

compound and the exact nature of the individual illness, doses outside this range may be prescribed by the attending physician. The oral route of administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, the preferred route of administration will be parenteral (i.m., i.v.) or topical.

The compounds of the present invention are generally administered in the form of pharmaceutical compositions comprising at least one of the compounds of the formula (I), together with a pharmaceutically acceptable vehicle or diluent in a ratio of 1:20 to 20:1 respectively. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration: for oral administration, in the form of tablets, hard or soft gelatin capsules, suspensions, granules, powders and the like; for parenteral administration, in the form of injectable solutions or suspensions, and the like, and for topical administration, in the form of solutions, lotions. ointments, salves and the like.

The present invention is illustrated by the following examples, but is not limited to the details thereof.

All non-aqueous reactions were run under dry, oxygen free nitrogen for convenience and generally to maximize yields. All solvents/diluents were dried according to standard published procedures or purchased in a predried form. All reactions were stirred either magnetically or mechanically. NMR spectra are recorded at 300 MHz and are reported in ppm downfield from trimethylsilane. The NMR solvent was $CDCl_3$ unless otherwise specified. IR spectra are reported in micrometers, generally specifying only strong signals.

Example 1

(±)-3,4-Dihydro-6-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)ethyl)quinoline-2-(1H)-one

A mixture of 300 mg (1.23 mmol) of 4-hydroxy-4-(phenoxymethyl)piperidine hydrochloride, 409 mg (1.84 mmol) of 6-(2-chloroacetyl)-3,4-dihydroquinolin-2(1H)-one and 0.514 mL (0.373 g, 3.7 mmol) of triethylamine in 25 mL of acetonitrile was heated at 60°C overnight. The solvent was then removed in vacuo and the residues partitioned between water and ethyl acetate and the organic layer was washed again with water and with brine. The ethyl acetate layer was dried with brine and magnesium sulfate and the solvent was evaporated to give 3,4-dihydro-6-(1-oxo-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)ethyl) quinoline-2-(1H)-one as a brown solid which was used in the subsequent reduction step without further purification.

The above ketone was dissolved in 25 mL of absolute ethanol and 500 mg (13.1 mmol) of $NaBH_4$ was added portionwise over 20 min. The reaction mixture was stirred at room temperature for 4 hrs. and then the solvent was removed and the residues were partitioned between water and ethyl acetate. After drying, the ethyl acetate was removed in vacuo and the residue was chromatographed on silica gel to give the product, 73 mg (15%), m.p. 186-188°C. NMR (CD_3OD) δ 1.70-2.10 (4H, m), 2.52-3.07 (10H, m), 3.33 (2H, s), 3.83 (2H, s), 6.82-7.38 (8H, m).

Example 2

(±)-5-(1-Hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)-piperidinyl)ethyl)benzimidazolin-2-one

Following the procedure of Example 1, the present title compound was obtained from 4-hydroxy-4-(phenoxymethyl)piperidine hydrochloride (1.23 mmol), 5-(2-chloroacetyl)-2-hydroxybenzimidazole (1.84 mmol) and triethylamine (3.7 mmol) in 25 ml of acetonitrile. The resulting ketone was stirred with sodium borohydride (13.1

mmol) in absolute ethanol to yield the desired compound after chromatography on silica gel. Yield 35%, m.p. 232-235°C. Anal. Calcd. for $C_{21}H_{25}N_3O_4 \cdot H_2O$: C, 62.81; H, 6.77; N, 10.46. Found: C, 62.98; H, 6.54; N, 10.32.

Example 3

(±)-5-(1-Hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)-piperidinyl)ethyl)-2-oxindole

Following the procedure of Example 1, the present title compound was obtained from 4-hydroxy-4-(phenoxymethyl)piperidine hydrochloride (1.23 mmol), 5-(2-chloroacetyl)oxindole (1.84 mmol) and triethylamine (3.7 mmol) in 25 ml of acetonitrile. The resulting ketone was stirred with sodium borohydride (13.1 mmol) in absolute ethanol to yield the desired compound after chromatography on silica gel. Yield 40%, m.p. 171-174°C.

Example 4

(±)-Erythro-5-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl) piperidinyl)propyl)benzimidazolin-2-one

A solution of 933 mg (2.36 mmol) of (±)-1-(5-(2-hydroxybenzimidazolyl))-2-(1-(4-hydroxy-4-phenoxymethyl) piperidinyl)propan-1-one in 10 mL of glacial acetic acid and 50 mL of absolute ethanol was treated portionwise with 944 mg (17.48 mmol) of potassium borohydride between 15-20°C and the resulting solution was stirred overnight at room temperature. The reaction mixture was then evaporated to dryness and the residues taken up in minimal water. The pH of this solution was adjusted to 7-8 with solid $NaHCO_3$, precipitating a solid. This material was insoluble in chloroform and relatively insoluble in ethyl acetate. The whole was again evaporated to dryness and the residues, which had crystallized, were taken up in ethanol and filtered to remove salts. The ethanol was evaporated and the residue taken up in isopropanol and treated with HCl gas in ether to precipitate a non-

crystalline salt which was separated by filtration and dried in a stream of dry nitrogen. This material was dissolved in hot ethyl acetate with methanol and clarified with decolorizing charcoal and then the methanol was boiled off. Cooling gave a colorless crystalline product, 410 mg (40%), m.p. 254-255°C. IR (KBr) 5.90 μm; NMR (CD_3OD) δ 1.22 (3H, d, J=7), 1.95-2.09 (2H, m), 2.15-2.30 (2H, m), 3.42-3.76 (4H, m), 3.91 (2H, s), 5.47 (1H, s), 6.92-7.35 (8H, m).

Example 5

(±)-Threo-5-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)-piperidinyl)propyl)benzimidazolin-2-one:

A total of 700 mg (18.4 mmol) of sodium borohydride was added portionwise to a suspension of 325 mg (0.82 mmol) of (±)-1-(5-(2-hydroxybenzimidazolyl)-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propan-1-one in 20 mL of absolute ethanol and the reaction mixture was stirred overnight at room temp. The solvent was then evaporated and the residual foam was taken up between ethyl acetate and water and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate extracts were dried and evaporated and the residual foam was chromatographed on silica gel using 1:1 ethanol/ethyl acetate to give the product as a white solid, m.p.>250°C. NMR (Acetone-d_6) δ 0.79 (3H, d, J=7), 1.71-1.88 (2H, m), 11.90-2.08 (2H, m), 2.48-2.88 (4H, m), 3.01 (1H, t, J=7), 3.88 (2H, s), 4.26 (1H, d, J=7), 6.86-7.32 (8H, m); Anal. Calcd for $C_{22}H_{27}N_3O_4.1.5\ H_2O$:C, 62.24; H, 7.12; N, 9.89. Found: C, 61.72; H, 6.73; N, 9.03.

Example 6

(±)-Erythro-3,4-dihydro-6-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propyl)quinolin-2(1H)one:

A solution of 7.13 g (17.5 mmol) of (±)-1-(6-(1,2,3,4-tetrahydro-2-oxoquinolinyl))-2-(1-(4-hydroxy-4-

phenoxymethyl)piperidinyl)propan-1-one in 135 mL of absolute ethanol and 70 mL of glacial acetic acid was treated portionwise with 6.22 g (115 mmol) of KBH_4 at 15-20°C and was then allowed to warm to room temperature for 30 min. The reaction mixture was evaporated to dryness and the residue was taken up in ice and cold water and this was basified with solid $NaHCO_3$. The solid which precipitated was separated by filtration, washed with water and air dried to give 3.66 g of crystalline free base, m.p. 192-196°C. The filtrate was extracted with ethyl acetate and the combined extracts were dried with brine and with $MgSO_4$ and evaporated to give an additional 786 mg of product (total yield 62%). A 510 mg sample of this material was dissolved in ethyl acetate and treated with a solution of HCl gas in ether to give 475 mg of the crystalline hydrochloride salt, m.p. 214-216°C (dec). IR (KBr) μm; NMR (CD_3OD) δ 1.15 (3H, d, J=7), 1.86-2.04 (2H, m), 3.52-3.66 (2H, m), 3.69-3.80 (1H, m), 3.86 (2H, s), 5.34 (1H, s), 6.81-6.96 (4H, m), 7.17-7.28 (4H, m).

Example 7

(±)-Threo-3,4-dihydro-6-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propyl)quinolin-2(1H)one:

A total of 1.50 g (39.5 mmol) of $NaBH_4$ was added portionwise to a suspension of 700 mg (1.71 mmol) of (±)-1-(5-(2-hydroxybenzimidazolyl))-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propan-1-one in 20 mL of absolute ethanol and the reaction mixture was stirred overnight at room temperature. The solvent was then evaporated and the residual foam was taken up between ethyl acetate and water and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried and evaporated and the residual foam was chromatographed on silica gel using 1:1 ethanol/ethyl acetate to give the product as a white solid, m.p. 192-196°C. A small amount of the erythro compound was formed in this reduction and could be separated from the column.

NMR (CD_3OD) δ 0.82 (3H, d, J=7), 1.72-2.06 (4H, m), 2.50-2.82 (6H, m), 2.88-3.02 (2H, t, J=7), 3.02 (1H, t, J=7), 3.84 (2H, s), 4.28 (1H, d, J=7), 6.80-7.34 (8 H, m); Anal. Calcd for $C_{22}H_{27}N_3O_4.1.5\ H_2O$:C, 65.88; H, 7.60; N, 6.40. Found: C, 65.74; H, 7.09; N, 6.31.

Example 8

(±)-Erythro-5-(1-hydroxy-2-(1-(4-hydroxy-4-phenoxymethyl) piperidinyl)propyl)oxindole

A mixture of 0.5 g (2.05 mmol) of 4-hydroxy-4-phenoxymethyl)piperidine hydrochloride, 0.5 g (2.25 mmol) of 5-(2-chloropropionyl)oxindole and 1 ml (0.725 g, 7.18 mmol) triethylamine in 20 mL of acetonitrile was refluxed for 24 h. The solvent was then removed in vacuo and the residues were partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine and was dried over $MgSO_4$ and concentrated to yield the ketone as a tan foam which was used for the following reaction without further purification, 537 mg (66%).

A solution of 500 mg (1.26 mmol) of the ketone in 20 mL of ethanol was treated portionwise with 1.0 g (26.3 mmol) of $NaBH_4$ and the resulting mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residues were partitioned between ethyl acetate and water. The ethyl acetate layer was washed and dried with brine and $MgSO_4$ and then evaporated to dryness. The residues were chromatographed on silica gel using ethyl acetate and gradually increasing concentrations of ethanol to give the threo product in pure fractions, 121 mg (24%), m.p. 204-207°C. NMR (DMSO-d_6) δ 0.70 (3H, d, J=7), 1.58-1.92 (4H, m), 2.40-2.65 (4H, m), 2.86 (1H, m), 3.32-3.40 (2H, m), 3.79 (2H, s), 4.20 (1H, d, J=7), 6.70-7.35 (8H, m), 10.34 (1H, s).

Example 9

(±)-1-(6-(1,2,3,4-Tetrahydro-2-oxoquinolinyl))-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propan-1-one

A suspension of 8.30 g (34.06 mmol) of 4-hydroxy-4-phenoxymethylpiperidine hydrochloride and 8.09 g (34.06 mmol) of 6-(2-chloro-1-propionyl)-1,2,3,4-tetrahydroquinolin-2(1H)-one in 100 mL of acetonitrile was treated with 16.61 mL (12.04 g, 0.12 mol) of triethylamine and the mixture was heated at reflux for 3 h and then stirred overnight at room temperature.

The reaction mixture was poured into water and extracted 3 times with ethyl acetate and the combined extracts were dried with brine solution and magnesium sulfate and evaporated to give a foam. This foam was dissolved in hot methanol and ethyl acetate and cooled to give a tan solid which was found to be starting chloroketone and discarded. The filtrates were evaporated and dissolved in ethyl acetate and ether was added to facilitate crystallization. The product was filtered and washed with ether to give 8.84 g (63.6%) of the product as a cream-colored solid, m.p. 137-139°C. The analytical sample was crystallized from hot ethyl acetate. NMR (CD_3OD) δ 1.28 (3H, d, J=7), 1.60-1.92 (4H, m), 2.52-2.84 (6H, m), 3.00 (2H, t, J=7), 3.75 (2H, s), 4.22 (1H, q, J=7), 6.82-7.00 (4H, m), 7.16 (2H, m), 7.82-7.98 (2H, m); Anal. Calcd for $C_{24}H_{28}N_2O_4$:C, 70.56; H, 6.91; N, 6.86. Found: C, 70.16; H, 6.78; N, 6.76.

Example 10

(±)-1-(5-(2-Hydroxybenzimidazolyl))-2-(1-(4-hydroxy-4-phenoxymethyl)piperidinyl)propan-1-one

A suspension of 2.43 g (10.0 mmol) of 4-hydroxy-4-phenoxymethylpiperidine hydrochloride and 2.25 g (10.0 mmol) of 5-(2-chloro-1-propionyl)-2-hydroxybenzimidazole in 40 mL of acetonitrile was treated with 4.88 mL (3.53 g, 35.0 mmol) of triethylamine and the reaction mixture was

heated at reflux for 90 min and then let sit over a weekend at room temperature.

The reaction mixture was then poured into a mixture of water and ethyl acetate and the resulting suspended solid was separated by filtration and found to be pure product, 1.15 g after drying. The filtrate was adjusted to pH=7.0 and extracted with ethyl acetate several times to give, after drying with brine solution and $MgSO_4$, a colorless solid which was recrystallized from hot ethyl acetate/methanol to give an additional 560 mg of product (total yield, 43%), m.p. 230-235°C (dec.). NMR (CD_3OD/DMSO-d_6) δ 1.29 (2H, d, J=7), 1.60-1.92 (4H, m), 2.54-2.84 (4H, m), 3.77 (2H, s), 4.26 (1H, q, J=7), 6.86-7.10 (6H, m), 7.75-7.92 (2H, m).

Example 11

(±)-1-(5-(Oxindolyl))-2-(1-(4-hydroxy-4-phenoxymethyl) piperidinyl)propan-1-one

Following the procedure of preparation 10, the present title compound was obtained from 4-hydroxy-4-phenoxymethylpiperidine hydrochloride (10.0 mmol), 5-(2-chloropropionyl)oxindole (10 mmol) and triethylamine (35 mmol) in 50 ml of acetonitrile. The title compound was isolated by crystallization from hot ethyl acetate/methanol to give an amorphous foam. Yield 66.4%. NMR ($CDCl_3$) δ 1.28 (3H, d, J=7), 1.58-1.78 (4H, m), 2.40-2.84 (4H, m), 3.54 (2H, s), 3.76 (2H, s), 4.09 (1H, q, J=7), 6.78-6.96 (3H, m), 7.14-7.26 (2H, m), 7.84-8.05 (3H, m), 9.52 (1H, broad s), 9.64 (1H, broad s).

Preparation 1

3,4 Dihydroquinolin-2-(1H)-one

A slurry of 50.0 g (0.259 mol) of o-nitrocinnamic acid in 500 mL of ethanol was treated with 5 teaspoons of Raney Ni and hydrogenated on a Parr shaker overnight at an initial pressure of 50 psi. In the morning, the pressure was increased again to 50 psi and the reaction was continued for an additional 5 h. The reaction mixture was filtered to remove the catalyst and then washed through a bed of silica gel with a mixture of ethyl acetate and ethanol to remove traces of nickel salts. Evaporation of the filtrate gave the desired product in 57% yield. NMR (DMSO-d_6) δ 2.45 (2H, t, J=7), 2.87 (2H, t, J=7), 6.87 (2H, d of d, J=7, 7), 7.12 (2H, d of d, J=7, 10), 10.08 (1H, s). m.p. 165-166°C.

Preparation 2

6-(2-Chloropropionyl)-3,4-dihydroquinolin-2-(1H)-one

A suspension of 72.5 g (0.544 mol) of $AlCl_3$ in 800 mL of CS_2 was stirred under dry N_2 while 14.1 mL (20.0 g, 0.177 mol) of 2-chloropropionyl chloride was added followed by 20.0 g (0.136 mol) of 3,4-dihydroquinolin-2(1H)-one. The reaction mixture was refluxed for 4 h at which time a separation of phases was noted. The reaction was quenched by pouring onto ice with vigorous stirring. The pale yellow precipitate which formed was separated by filtration, washed with water and dried overnight over P_2O_5 to give 27.7 g (91%) of the desired product, m.p. 236.5-238°C.

Preparation 3

5-(2-Chloropropionyl)-2-hydroxybenzimidazole

Following the procedure of Preparation 2, the present title compound was obtained from 2-hydroxybenzimidazole (0.136 mol), aluminum chloride (0.544 mol) and 2-chloropropionyl chloride (0.177 mol) in 800 ml CS_2. The

title compound was isolated by filtration. Yield 92%, m.p. 245° dec. Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47. Found C, 54.41; H, 4.07; N, 13.25.

Preparation 4

5-(2-Chloropropionyl)oxindole

Following the procedure of Preparation 2, the present title compound was obtained from oxindole (0.136 mol), aluminum chloride (0.544 mol) and 2-chloropropionyl chloride (0.177 mol) in 800 ml CS_2. The title compound was isolated by filtration. Yield 91%, m.p. 157-158°C.

Preparation 5

6-(2-Chloroacetyl)-3,4-dihydroquinolin-2(1H)-one

Following the procedure of Preparation 2, the present title compound was obtained from 3,4-dihydroquinolin-2-(1H)-one (0.136 mol), aluminum chloride (0.544 mol) and 2-chloroacetyl chloride (0.177 mol) in 800 ml CS_2. The title compound was isolated by filtration. Yield 50%, m.p. 215-216°C.

Preparation 6

5-(2-Chloroacetyl)-2-hydroxybenzimidazole

Following the procedure of Preparation 2, the present title compound was obtained from 2-hydroxybenzimidazole (0.136 mol), aluminum chloride (0.544 mol) and 2-chloroacetyl chloride (0.177 mol) in 800 ml CS_2. The title compound was isolated by filtration. Quantitative yield, m.p. 273-275°C (dec).

Preparation 7

5-(2-Chloroacetyl)-oxindole

Following the procedure of Preparation 2, the present title compound was obtained from oxindole (0.136 mol), aluminum chloride (0.544 mol) and 2-chloroacetyl chloride

(0.177 mol) in 800 ml CS_2. The title compound was isolated by filtration. Yield 90%, m.p. 236.5-239°C.

Preparation 8

4-Hydroxy-4-phenoxymethylpiperidine hydrochloride

Oil free sodium hydride (2.16 g, 0.09 M) was added to dry dimethyl sulfoxide (250 mL) under nitrogen gas and the mixture was heated to 60-65°C until a uniform black solution was formed, about 1 h. Then 19.83 g (0.09 M) of trimethylsulfoxonium iodide was added (slight exotherm) and the mixture was stirred until a brown solution occurred, about 30 min. Then a solution of 13.40 g (67.3mM) of N-t-butyloxycarbonyl-4-piperidone in 50 mL of dimethyl sulfoxide was stirred at room temperature for 1 h. The reaction mixture was then poured into 1 L of cold water and the whole was extracted 4X with 100 mL portions of hexane. The combined hexane extracts was back-washed with 50 mL of water and with brine solution and was dried with magnesium sulfate, filtered and evaporated to give 11.75 g of white crystalline product, 6-t-butyloxycarbonyl-1-oxa-6-azaspiro[2.5]octane, (78% yield).

Further extraction of the aqueous layers with 3X 50 mL of hexane gave a further 650 mg of product for a total yield of 82.5%.

m.p. 57.5-59.5°C; IR(KBr) 5.90 μm; NMR δ 1.32-1.48 (2H, m), 1.42 (9H, s), 1.74-1.80 (2H, m), 2.65 (2H, s), 3.31-3.43 (2H, m), 3.61-3.72 (2H, m); Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.05; H, 9.09; N, 6.58.

A solution of 10.37 g (0.11 M) of phenol in 100 mL of dry dimethyl sulfoxide treated portionwise with 1.99 g (82.8 mmol) of oil-free sodium hydride keeping the temperature between 20-25°C with a cold water bath. The reaction mixture was then stirred at room temperature for 45 min to give a grey suspension. The 11.75 g (55.2 mmol) of 6-t-butyloxycarbonyl-1-oxa-6-azaspiro[2.5]octane dissolved in 65 mL of dimethyl sulfoxide was added

dropwise after which the reaction mixture was heated to 55-60°C for 7 h and was then stirred at room temperature overnight.

The reaction mixture was then poured into 1 L of cold water and extracted 4X with ether. The combined ether extracts was backwashed with 10% NaOH and with brine and was dried with magnesium sulfate evaporated to give the desired product, N-t-butyloxycarbonyl-4-hydroxy-4-phenoxymethylpiperidine, as an oil weighing 17.01 g (100%).

IR (Film) 5.91, 2.95 μM; NMR ($CDCl_3$) δ 1.46 (9H, s); 1.53-1.80 (4H, m), 3.13-3.30 (2H, m), 3.80 (2H, s), 3.80-3.98 (2H, m), 6.84-6.99 (2H, m), 7.22-7.44 (3H, m); Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 65.72; H, 8.21; N, 4.77.

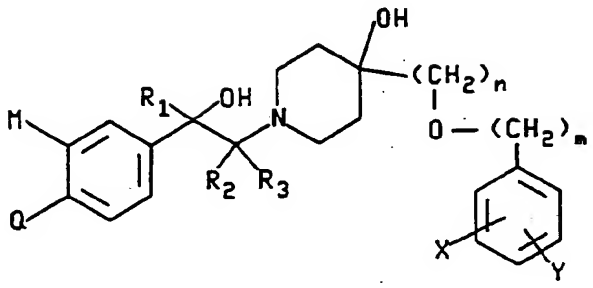
A solution of 17.0 g (0.055 M) of N-t-Butyloxycarbonyl-4-hydroxy-4-phenoxymethylpiperidine in 150 mL of methanol was saturated with HCl gas. After the mixture had cooled, it was again treated with HCl gas and this procedure was again repeated. After crystals had formed, the reaction mixture was treated with 500 mL of anhydrous ether and let stir at room temperature overnight.

The product was filtered and washed with dry ether and dried under a stream of dry N_2 to give 10.85 g (80.6%) of crystalline material, m.p. 202-204°C. IR (KBr) 3.06, 3.14, 3.44, 3.57, 3.56, 6.33, 8.06 μm; NMR (D_2O) δ 2.00 (4 H, broad s), 3.34 (4H, broad s), 4.00 (2H, s), 6.98-7.09 (3H, m), 7.30-7.43 (2H, m). Anal. Calcd for $C_{12}H_{17}NO_2$.HCl: C, 59.13; H, 7.44; N, 5.75. Found: C, 58.98; H, 7.11; N, 5.65.

CLAIMS

I claim:

1. A compound of the formula:



(I)

and the pharmaceutically-acceptable salts thereof; wherein R_1, R_2 and R_3 are each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, amino, nitro and alkoxy having 1 to 4 carbons;
or R_1 and R_2 when taken together form a methylene, ethylene, propylene or butylene group;
m is 0 to 2;
n is 1 or 2;
X and Y are each selected from the group consisting of hydrogen, chloro, bromo, fluoro, trifluoromethyl, alkoxy having 1 to 4 carbons, alkyl having 1 to 4 carbons, hydroxy, amino, nitro and substituted phenoxy, wherein the substituent on said substituted phenoxy is selected from the group consisting of hydrogen, hydroxy, alkyl

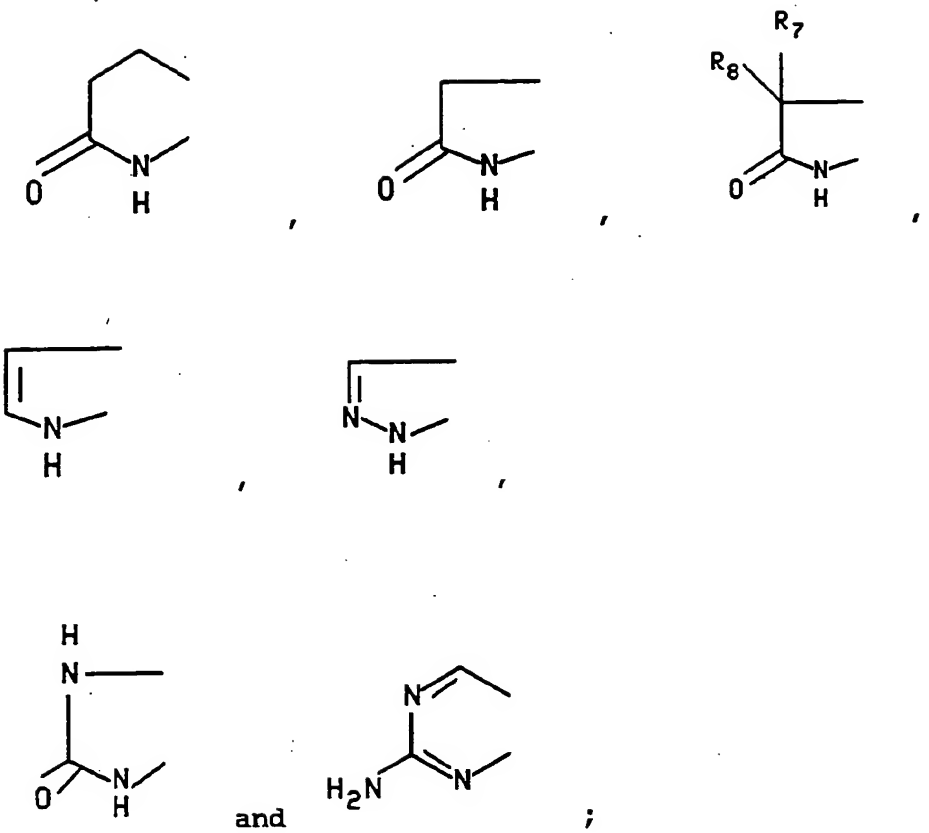
having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, nitro, amino and alkoxy having 1 to 4 carbons;

M and Q are each selected from the group consisting of hydrogen, hydroxy, amino, chloro, bromo, fluoro, trifluoromethyl, nitro, alkyl having 1 to 4 carbons, alkoxy having 1 to 4 carbons, N,N-dialkylamino having 1 to 4 carbons in each of said alkyls, N-alkylamino having 1 to 4 carbons, $NHCOR_4$, $NHCOOR_5$ and $NHSO_2R_6$;

wherein R_4 is selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

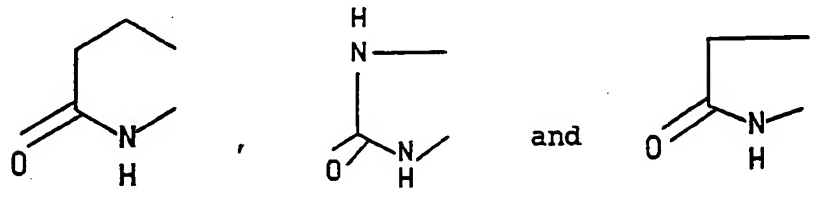
and wherein R_5 and R_6 are each selected from the group consisting of alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

or M and Q when taken together form a divalent radical Z, wherein Z is selected from the group consisting of



wherein R_7 and R_8 are each selected from the group consisting of hydrogen and methyl.

2. A compound according to claim 1, wherein R_2 is hydrogen; R_3 is hydrogen or methyl; and M and Q form the radical Z, wherein Z is selected from the group consisting of



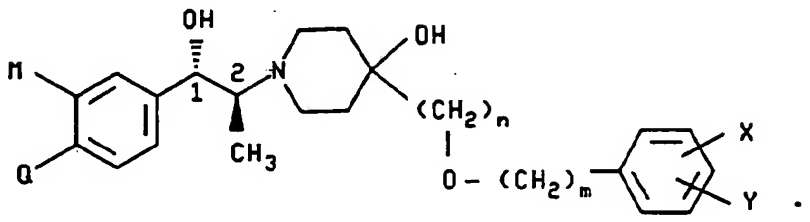
3. A compound according to claim 2, wherein n is 1 and m is 0.

4. A compound according to claim 3, wherein R_1 is hydrogen.

5. A compound according to claim 4, wherein R_3 is hydrogen.

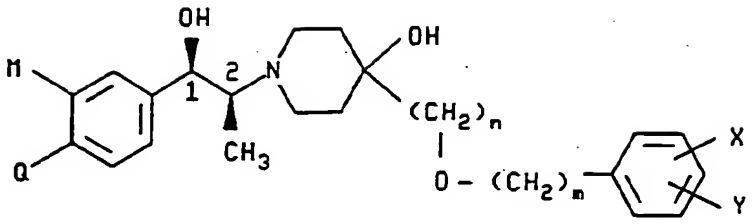
6. A compound according to claim 5, wherein X and Y are each hydrogen.

7. A compound according to claim 4 of the formula



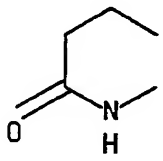
8. A compound according to claim 7, wherein X and Y are each hydrogen.

9. A compound according to claim 4 of the formula

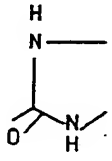


10. A compound according to claim 9, wherein X and Y are each hydrogen.

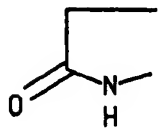
11. A compound according to claim 6, wherein Z is



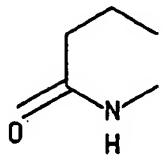
12. A compound according to claim 6, wherein Z is



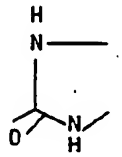
13. A compound according to claim 6, wherein Z is



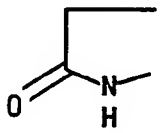
14. The compound according to claim 8, wherein Z is



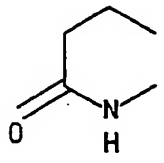
15. The compound according to claim 8, wherein Z is



16. The compound according to claim 8, wherein Z is



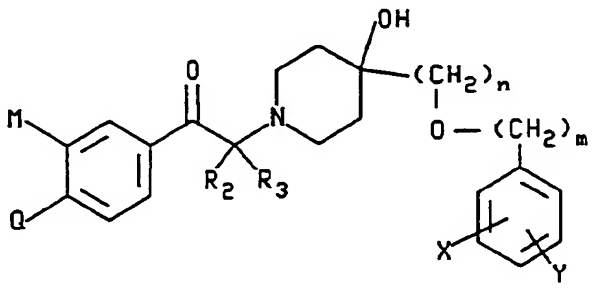
17. The compound according to claim 10, wherein Z is



18. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

19. A method of treating traumatic injury to the brain and spinal cord, stroke or a CNS degenerative disease in a human subject which comprises administering to said human subject a neuroprotective amount of a compound of claim 1.

20. A compound of the formula:



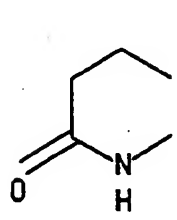
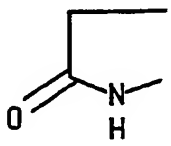
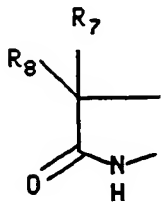
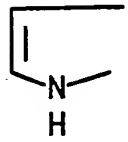
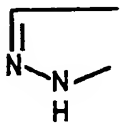
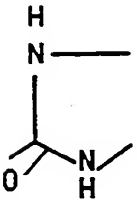
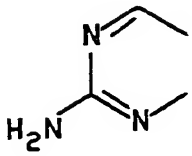
(IV)

wherein

R_2 and R_3 are each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said

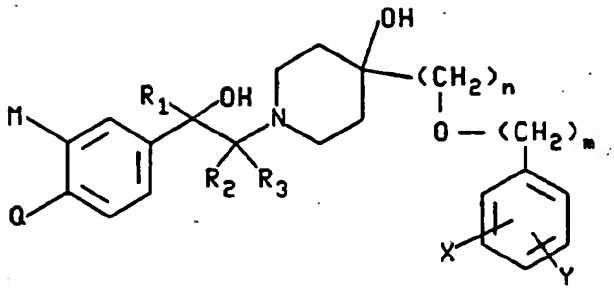
substituted phenyl is selected from the group consisting of hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, amino, nitro and alkoxy having 1 to 4 carbons;
m is 0 to 2;
n is 1 or 2;
X and Y are each selected from the group consisting of hydrogen, chloro, bromo, fluoro, trifluoromethyl, alkoxy having 1 to 4 carbons, alkyl having 1 to 4 carbons, hydroxy, amino, nitro and substituted phenoxy, wherein the substituent on said substituted phenoxy is selected from the group consisting of hydrogen, hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, nitro, amino and alkoxy having 1 to 4 carbons;
M and Q are each selected from the group consisting of hydrogen, hydroxy, amino, chloro, bromo, fluoro, trifluoromethyl, nitro, alkyl having 1 to 4 carbons, alkoxy having 1 to 4 carbons, N,N-dialkylamino having 1 to 4 carbons in each of said alkyls, N-alkylamino having 1 to 4 carbons, $NHCOR_4$, $NHCOOR_5$ and $NHSO_2R_6$;
wherein R_4 is selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;
and wherein R_5 and R_6 are each selected from the group consisting of alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

or M and Q when taken together form a divalent radical Z, wherein Z is selected from the group consisting of

and wherein R_7 and R_8 are each selected from the group consisting of hydrogen and methyl.

21. A process for a compound of the formula:



(I)

and the pharmaceutically-acceptable salts thereof; wherein R_1, R_2 and R_3 are each selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, amino, nitro and alkoxy having 1 to 4 carbons;

or R_1 and R_2 when taken together form a methylene, ethylene, propylene or butylene group;

m is 0 to 2;

n is 1 or 2;

X and Y are each selected from the group consisting of hydrogen, chloro, bromo, fluoro, trifluoromethyl, alkoxy having 1 to 4 carbons, alkyl having 1 to 4 carbons, hydroxy, amino, nitro and substituted phenoxy, wherein the substituent on said substituted phenoxy is selected from the group consisting of hydrogen, hydroxy, alkyl having 1 to 4 carbons, chloro, bromo, fluoro,

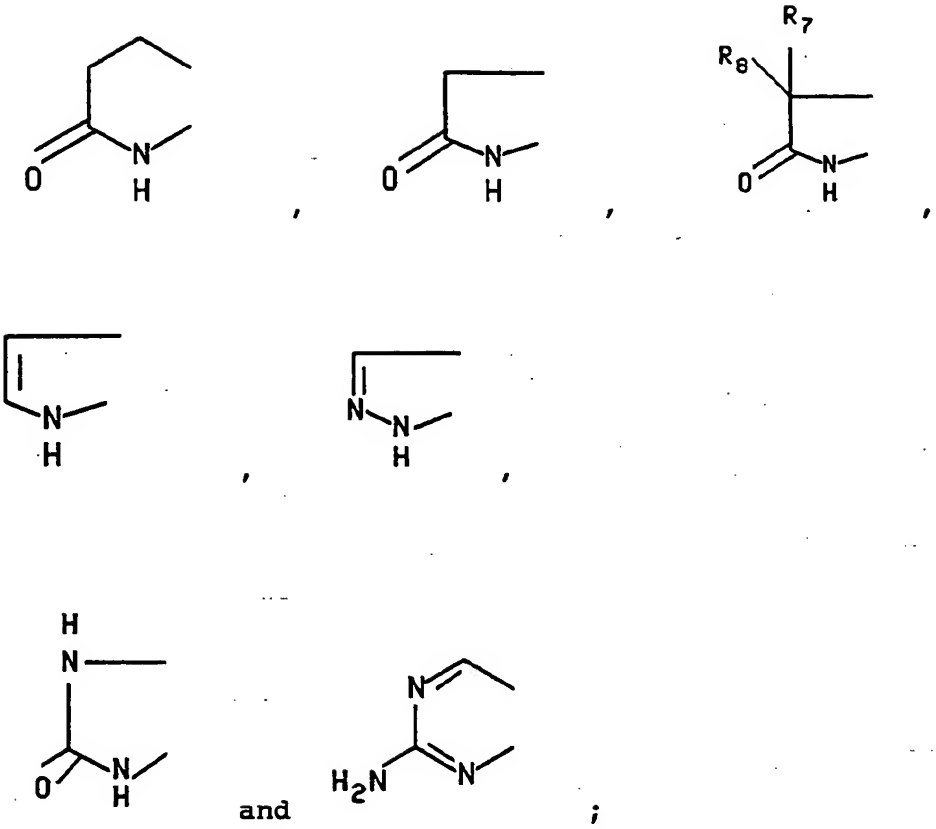
trifluoromethyl, nitro, amino and alkoxy having 1 to 4 carbons;

M and Q are each selected from the group consisting of hydrogen, hydroxy, amino, chloro, bromo, fluoro, trifluoromethyl, nitro, alkyl having 1 to 4 carbons, alkoxy having 1 to 4 carbons, N,N-dialkylamino having 1 to 4 carbons in each of said alkyls, N-alkylamino having 1 to 4 carbons, $NHCOR_4$, $NHCOOR_5$ and $NHSO_2R_6$;

wherein R_4 is selected from the group consisting of hydrogen, alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

and wherein R_5 and R_6 are each selected from the group consisting of alkyl having 1 to 6 carbons, phenyl and substituted phenyl, wherein the substituent on said substituted phenyl is selected from the group consisting of hydroxy, chloro, bromo, fluoro, trifluoromethyl, amino, nitro, alkyl having 1 to 4 carbons and alkoxy having 1 to 4 carbons;

or M and Q when taken together form a divalent radical Z, wherein Z is selected from the group consisting of



wherein R_7 and R_8 are each selected from the group consisting of hydrogen and methyl.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/04973

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 211/48 C 07 D 211/44 C 07 D 401/06
A 61 K 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 211/00 C 07 D 401/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

	Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
2	A	EP,A,0398578 (PFIZER) 22 November 1990, see entire document (cited in the application)	1-21
5	A	EP,A,0351282 (SYNTHELABO) 17 January 1990, see entire document (cited in the application)	1-21
6	A	GB,A,2071094 (OTSUKA) 16 September 1981, see entire document	1-21
7	A	FR,A,2546166 (SYNTHELABO) 23 November 1984, see entire document (cited in the application)	1-21
5	A,P	WO,A,9117156 (PFIZER) 14 November 1991, see entire document	1-21

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-09-1992	05. 10. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Nelson Wemberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/04973

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 19 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204973 SA 62195

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0398578	22-11-90	WO-A-	9014087	29-11-90
		CA-A-	2016860	17-11-90
		WO-A-	9014088	29-11-90
EP-A- 0351282	17-01-90	FR-A-	2634206	19-01-90
		FR-A-	2640266	15-06-90
		AU-B-	618378	19-12-91
		AU-A-	3802989	18-01-90
		JP-A-	2072173	12-03-90
		US-A-	5034401	23-07-91
GB-A- 2071094	16-09-81	JP-C-	1480423	10-02-89
		JP-A-	56125370	01-10-81
		JP-B-	63025585	26-05-88
		JP-C-	1478293	27-01-89
		JP-A-	57038772	03-03-82
		JP-B-	63020430	27-04-88
		AT-B-	387215	27-12-88
		AU-B-	523005	08-07-82
		AU-A-	6797381	10-09-81
		BE-A-	887800	07-09-81
		CA-A-	1155119	11-10-83
		CH-A-	647775	15-02-85
		DE-A,C	3107601	04-02-82
		DE-C-	3152880	22-03-90
		FR-A,B	2477542	11-09-81
		NL-A-	8101099	01-10-81
		NL-A-	8802223	02-01-89
		SE-B-	447255	03-11-86
		SE-A-	8101409	07-09-81
		SU-A-	1367857	15-01-88
		US-A-	4455422	19-06-84
		US-A-	4567187	28-01-86
		US-A-	4460593	17-07-84
		US-A-	4619932	28-10-86
FR-A- 2546166	23-11-84	None		
WO-A- 9117156	14-11-91	AU-A-	7456591	27-11-91

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204973 SA 62195

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 24/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9117156		CN-A- 1056497	27-11-91